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The axonal membrane protein Caspr, a homologue of neurexin IV, is a component of the septate-like paranodal junctions that assemble during myelination.

Einheber S, Zanazzi G, Ching W, Scherer S, Milner TA, Peles E, Salzer JL.

Department of Cell Biology, New York University Medical School, New York 10016, USA.

We have investigated the potential role of contactin and contactin-associated protein (Caspr) in the axonal-glial interactions of myelination. In the nervous system, contactin is expressed by neurons, oligodendrocytes, and their progenitors, but not by Schwann cells. Expression of Caspr, a homologue of Neurexin IV, is restricted to neurons. Both contactin and Caspr are uniformly expressed at high levels on the surface of unensheathed neurites and are downregulated during myelination in vitro and in vivo. Contactin is downregulated along the entire myelinated nerve fiber. In contrast, Caspr expression initially remains elevated along segments of neurites associated with nascent myelin sheaths. With further maturation, Caspr is downregulated in the internode and becomes strikingly concentrated in the paranodal regions of the axon, suggesting that it redistributes from the internode to these sites. Caspr expression is similarly restricted to the paranodes of mature myelinated axons in the peripheral and central nervous systems; it is more diffusely and persistently expressed in gray matter and on unmyelinated axons. Immunoelectron microscopy demonstrated that Caspr is localized to the septate-like junctions that form between axons and the paranodal loops of myelinating cells. Caspr is poorly extracted by nonionic detergents, suggesting that it is associated with the axon cytoskeleton at these junctions. These results indicate that contactin and Caspr function independently during myelination and that their expression is regulated by glial ensheathment. They strongly implicate Caspr as a major transmembrane component of the paranodal junctions, whose molecular composition has previously been unknown, and suggest its role in the reciprocal signaling between axons and glia.

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ELSEVIER SCIENCE FULL-TEXT ARTICLE

Neurexin IV, caspr and paranodin--novel members of the neurexin family: encounters of axons and glia.

Bellen HJ, Lu Y, Beckstead R, Bhat MA.

Dept of Human and Molecular Genetics, Howard Hughes Medical Institute, Baylor College of Medicine, Houston, TX 77030, USA.

Axonal insulation is of key importance for the proper propagation of action potentials. In Drosophila and other invertebrates, it has recently been demonstrated that septate junctions play an essential role in axonal insulation or blood-brain-barrier formation. Neurexin IV, a molecular component of Drosophila septate junctions, has been shown to be essential for axonal insulation in the PNS in embryos and larvae. Interestingly, a vertebrate homolog of Neurexin IV, caspr--also named paranodin--has been shown to localize to septate-like junctional structures.These vertebrate junctions are localized to the paranodal region of the nodes of Ranvier, between axons and Schwann cells. Caspr/paranodin might play an important role in barrier formation, and link neuronal membrane components with the axonal cytoskeletal network.

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1: Neuron 1999 Dec;24(4):1037-47

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Caspr2, a new member of the neurexin superfamily, is localized at the juxtaparanodes of myelinated axons and associates with K+ channels.

Poliak S, Gollan L, Martinez R, Custer A, Einheber S, Salzer JL, Trimmer JS, Shrager P, Peles E.

Department of Molecular Cell Biology, The Weizmann Institute of Science, Rehovot, Israel.

Rapid conduction in myelinated axons depends on the generation of specialized subcellular domains to which different sets of ion channels are localized. Here, we describe the identification of Caspr2, a mammalian homolog of Drosophila Neurexin IV (Nrx-IV), and show that this neurexin-like protein and the closely related molecule Caspr/Paranodin demarcate distinct subdomains in myelinated axons. While contactin-associated protein (Caspr) is present at the paranodal junctions, Caspr2 is precisely colocalized with Shaker-like K+ channels in the juxtaparanodal region. We further show that Caspr2 specifically associates with Kv1.1, Kv1.2, and their Kvbeta2 subunit. This association involves the C-terminal sequence of Caspr2, which contains a putative PDZ binding site. These results suggest a role for Caspr family members in the local differentiation of the axon into distinct functional subdomains.

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1: J Neurosci 2000 Nov 15;20(22):8354-64

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Contactin-associated protein (Caspr) and contactin form a complex that is targeted to the paranodal junctions during myelination.

Rios JC, Melendez-Vasquez CV, Einheber S, Lustig M, Grumet M, Hemperly J, Peles E, Salzer JL.

Department of Cell Biology, New York University School of Medicine, New York, New York 10016, USA.

Specialized paranodal junctions form between the axon and the closely apposed paranodal loops of myelinating glia. They are interposed between sodium channels at the nodes of Ranvier and potassium channels in the juxtaparanodal regions; their precise function and molecular composition have been elusive. We previously reported that Caspr (contactin-associated protein) is a major axonal constituent of these junctions (Einheber et al., 1997). We now report that contactin colocalizes and forms a cis complex with Caspr in the paranodes and juxtamesaxon. These proteins coextract and coprecipitate from neurons, myelinating cultures, and myelin preparations enriched in junctional markers; they fractionate on sucrose gradients as a high-molecular-weight complex, suggesting that other proteins may also be associated with this complex. Neurons express two contactin isoforms that differ in their extent of glycosylation: a lower-molecular-weight phosphatidylinositol phospholipase C (PI-PLC)-resistant form is associated specifically with Caspr in the paranodes, whereas a higher-molecular-weight form of contactin, not associated with Caspr, is present in central nodes of Ranvier. These results suggest that the targeting of contactin to different axonal domains may be determined, in part, via its association with Caspr. Treatment of myelinating cocultures of Schwann cells and neurons with RPTPbeta-Fc, a soluble construct containing the carbonic anhydrase domain of the receptor protein tyrosine phosphatase beta (RPTPbeta), a potential glial receptor for contactin, blocks the localization of the Caspr/contactin complex to the paranodes. These results strongly suggest that a preformed complex of Caspr and contactin is targeted to the paranodal junctions via extracellular interactions with myelinating glia.

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Localization of Caspr2 in myelinated nerves depends on axon-glia interactions and the generation of barriers along the axon.

Poliak S, Gollan L, Salomon D, Berglund EO, Ohara R, Ranscht B, Peles E.

Department of Molecular Cell Biology, The Weizmann Institute of Science, Rehovot 76100, Israel.

Cell recognition proteins of the contactin-associated protein (Caspr) family demarcate distinct domains along myelinated axons. Caspr is present at the paranodal junction formed between the axon and myelinating glial cells, whereas Caspr2 is localized and associates with K(+) channels at the adjacent juxtaparanodal region. Here we investigated the distribution of Caspr2 during development of peripheral nerves of normal and galactolipids-deficient [ceramide galactosyl transferase (CGT)-/-] mice. This mutant exhibits paranodal abnormalities, lacking all putative adhesion components of this junction, including Caspr, contactin, and neurofascin 155. In sciatic nerves of this mutant, Caspr2 was not found at the juxtaparanodal region but was concentrated instead at the paranodes with Kv1.2. Similar distribution of Caspr2 was found in the PNS of contactin knock-out mice, which also lack Caspr in their paranodes. During development of wild-type peripheral nerves, Caspr2 and Kv1.2 were initially detected at the paranodes before relocating to the adjacent juxtaparanodal region. This transition was not observed in CGT mice, where Caspr2 and Kv1.2 remained paranodal. Double labeling for Caspr and Caspr2 demonstrated that these two related proteins occupied mutually excluding domains along the axon and revealed the presence of both paranodal and internodal barrier-like structures that are delineated by Caspr. Finally, we found that the disruption of axon-glia contact in CGT-/- nerves also affects the localization of the cytoskeleton-associated protein 4.1B along the axon. Altogether, our results reveal a sequential appearance of members of the Caspr family at different domains along myelinated axons and suggest that the localization of Caspr2 may be controlled by the generation of Caspr-containing barriers along the axon.

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1: J Cell Biol 2002 Jun 24;157(7):1247-56

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Retention of a cell adhesion complex at the paranodal junction requires the cytoplasmic region of Caspr.

Gollan L, Sabanay H, Poliak S, Berglund EO, Ranscht B, Peles E.

Department of Molecular Cell Biology, The Weizmann Institute of Science, Rehovot 76100, Israel.

An axonal complex of cell adhesion molecules consisting of Caspr and contactin has been found to be essential for the generation of the paranodal axo-glial junctions flanking the nodes of Ranvier. Here we report that although the extracellular region of Caspr was sufficient for directing it to the paranodes in transgenic mice, retention of the Caspr-contactin complex at the junction depended on the presence of an intact cytoplasmic domain of Caspr. Using immunoelectron microscopy, we found that a Caspr mutant lacking its intracellular domain was often found within the axon instead of the junctional axolemma. We further show that a short sequence in the cytoplasmic domain of Caspr mediated its binding to the cytoskeleton-associated protein 4.1B. Clustering of contactin on the cell surface induced coclustering of Caspr and immobilized protein 4.1B at the plasma membrane. Furthermore, deletion of the protein 4.1B binding site accelerated the internalization of a Caspr-contactin chimera from the cell surface. These results suggest that Caspr serves as a "transmembrane scaffold" that stabilizes the Caspr/contactin adhesion complex at the paranodal junction by connecting it to cytoskeletal components within the axon.

PMID: 12082082 [PubMed - indexed for MEDLINE]

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1: Mol Cell Neurosci 2002 Jun;20(2):283-97

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ELSEVIER SCIENCE
FULL-TEXT ARTICLE

Caspr3 and caspr4, two novel members of the caspr family are expressed in the nervous system and interact with PDZ domains.

Spiegel I, Salomon D, Erne B, Schaeren-Wiemers N, Peles E.

Department of Molecular Cell Biology, The Weizmann Institute of Science, Rehovot 76100, Israel.

The NCP family of cell-recognition molecules represents a distinct subgroup of the neurexins that includes Caspr and Caspr2, as well as Drosophila Neurexin-IV and axotactin. Here, we report the identification of Caspr3 and Caspr4, two new NCPs expressed in nervous system. Caspr3 was detected along axons in the corpus callosum, spinal cord, basket cells in the cerebellum and in peripheral nerves, as well as in oligodendrocytes. In contrast, expression of Caspr4 was more restricted to specific neuronal subpopulations in the olfactory bulb, hippocampus, deep cerebellar nuclei, and the substantia nigra. Similar to the neurexins, the cytoplasmic tails of Caspr3 and Caspr4 interacted differentially with PDZ domain-containing proteins of the CASK/Lin2-Veli/Lin7-Mint1/Lin10 complex. The structural organization and distinct cellular distribution of Caspr3 and Caspr4 suggest a potential role of these proteins in cell recognition within the nervous system. (c) 2002 Elsevier Science (USA).

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